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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,126	03/14/2001	Torben Halkier	3631-0108P	6308

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,126	HALKIER ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,8-12,17-24,28 and 57-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,8-12,17-24,28 and 57-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050222*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner: Xiaozhen Xie.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The Information Disclosure Statement (IDS) filed 22 February 2005 has been entered. Applicant's amendment of the claims filed 29 July 2005 is acknowledged.

Claim 3 has been cancelled. Claims 61-87 have been added. Claims 1, 5, 8-12, 17-24, 28 and 57-87 are pending and under examination in this office action.

Claim Rejections Maintained

Claims 1, 5, 8-12, 17-24, 28 and 57-60 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U. S. Patent No: 6,645,500. This rejection also applies to the newly added claims 61-87 for reasons set forth in the previous office action (31 January 2005).

Applicant indicated that the rejection will be addressed upon the indication of allowable subject matter in the present application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 8-12, 17-24, 28 and 57-60 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for in vivo down-regulation of OPGL activity in a mammal, the method comprising effecting presentation to the mammal's immune system of an immunologically effective amount of at least one modified mammalian OPGL polypeptide or analogue thereof which has a result that immunization of the mammal with the modified mammalian OPGL polypeptide or analogue thereof induces production of antibodies against the mammal's own OPGL polypeptide which down-regulates the mammals own OPGL activity, wherein said modified mammalian OPGL polypeptide or analogue thereof comprising at least residues 158 to 136 of OPGL and is modified by the introduction of immunogenic amino acid sequences which are introduced such that inherent B-cell epitopes in said OPGL polypeptide or analogue thereof are preserved, does not reasonably provide enablement for other permutations of the claimed formula, substitutions, mutations, insertions, deletions, and alterations of the amino acid sequence SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. This rejection also applies to the newly added claims 62-87.

Applicant argues that the amended claims require that at least one B-cell epitope in a mammalian OPGL and at least one foreign T-helper epitope (either as a side group

in one of the $OPGL_{ex}$ fragments or as one of the MOD fragments) are present in the formula (I), and that the requirement for the presence of the minimal number of components won't destroy the protein functionality because the introduction of amino acid modifications, nor affect the immunological responses. Applicant argues that identification of B-cell epitopes in a known protein antigen is not problematic and can be achieved either *in silico* or *in vitro* by simple epitope mapping. With regard to the structure and position of epitope placement for the modified OPGL, Applicant argues that the modifications are "introduced between the preserved B-cell epitopes". Applicant further argues that an OPGL immunogen targeting other parts of the molecule rather than the active domain of OPGL (amino acid residues 158-316 for murine OPGL and amino acid residues 159-317 for human OPGL) can also result in the immunological responses, i.e., clearance of the antigen.

Applicant's arguments have been fully considered but have not been found to be persuasive for reasons set forth in the previous office action and for the following reasons.

The instant invention encompasses the introduction of modifications or immunogenic amino acid sequences (epitopes) into human OPGL (SEQ ID NO: 2) resulting in an immunogenic OPGL protein. This modified protein is then administered to a mammal such that the endogenous OPGL is immunologically suppressed (cleared) due to the production of antibodies against the mammal's own OPGL, and resulted in a lower level of OPGL. The specification teaches OPGL as a negative regulator of osteoclasts which promote bone resorption, and that immunogens capable of inducing

antibodies cross-reactive with self-OPGL can be used in a method for down-regulation of OPGL whereby diseases such as osteoporosis can be treated. The specification, however, does not provide guidance as to how to make and use the modified OPGL immunogens as broadly claimed as in the formulas (claims 1, 65, 67 and 75). The formulas require: x number of OPGL fragments, identical or non-identical, which are presented as B-cell epitopes, with or without foreign side group in the form of at least one T-helper lymphocyte epitope, and require x number of modifications in the form of at least one T-helper lymphocyte epitope. The claims do not limit the numbers of B-cell epitopes in a mammalian OPGL and foreign T-helper epitopes. Applicant's argument that "at least one B-cell epitope in a mammalian OPGL and at least one foreign T-helper epitope (either as a side group in one of the $OPGL_{ex}$ fragments or as one of the MOD fragments) are present in the formulas", does not provide sufficient guidance as to how many B-cell epitopes that contain subsequences of OPGL, and foreign T-helper epitopes are required, so that the synthesized molecules are effective in promoting the immune responses when administered into a mammal. In addition, the specification does not identify all the B-cell epitopes in a mammalian OPGL. Applicant argues that identification of B-cell epitopes in a known protein antigen can be achieved either *in silico* or *in vitro* by simple epitope mapping. However, the disclosure of an invention is to teach how to "make and use", rather than "make and test". As for the T-helper epitopes, simply reciting "introduced between the preserved B-cell epitopes" does not provide sufficient teachings as to what these OPGL B-cell epitopes are, how long these fragments encompass, nor teaches which side groups are modified, whether additional

T-helper epitopes are required if side groups are modified. As for the argument that an OPGL immunogen targeting other parts of the molecule rather than the active domain of OPGL (amino acid residues 158-316 for murine OPGL and amino acid residues 159-317 for human OPGL) can also results in the immunological responses. Again, the specification does not teach which parts of the OPGL molecule can be used to generate the immune response, since the specification clearly stated that it is logical to direct the autoantibodies against this part of OPGL (amino acid residues 158-316 for murine OPGL and amino acid residues 159-317 for human OPGL).

Thus, without detailed guidance as to the nature of the modified OPGL immunogen, the artisan would be unable to identify and use such molecules for in vivo down regulation of OPGL activity in a mammal or for treating or preventing excessive bone loss in a patient. Since the specification does not teach the correlation of structure/function, one of skill in the art would evaluate all non-exemplified OPGL-B-cell moiety combinations and modifications for down-regulating OPGL activity in vivo. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of modified OPGL immunogens comprising a vast number of different combinations of B-cell epitopes of human OPGL protein which further containing modifications on side groups or between the B-cell epitopes, as recited in the claims, and screen same for in vivo down regulation of OPGL activity in a mammal or for treating or preventing excessive bone loss in a patient, the lack of direction/guidance

presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of protein structure changes on biological activity and immunogeneicity, and the breadth of the claims which fails to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1, 5, 8-12, 17-24, 28 and 57-60 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection also applies to the newly added claims 62-87.

Applicant argues that amended claim 1 does define the claimed genus in terms of: a) the "starting" OPGL is SEQ ID NO: 2 for human OPGL protein; b) the modified OPGL polypeptide has modifications, which are introduced "between the preserved B-cell epitopes"; c) the modified OPGL polypeptide has at least one modification "in the form of at least one foreign T-helper lymphocyte epitope; and d) the modified OPGL polypeptide functions by inducing antibodies which bind to the animal's own OPGL, thereby down-regulating OPGL. Applicant argues that the claims recite a combination of structural and functional characteristics that sufficiently define Applicant's generic invention.

Applicant's arguments have been fully considered but have not been found to be persuasive for reasons set forth in the previous office action and for the reasons discussed above.

The claims recite combinations of B-cell epitopes containing subsequences of OPGL with various changes. The claims do not require the entity to possess any particular conserved structure, or other distinguishing features. The claims are drawn to a myriad of possible B-cell epitopes/OPGL combinations and further modifications. There is no teaching as to the correlation of structure/function. There is no disclosure of complete or partial structure, physical and/or chemical properties, or methods of making of the claimed product. Merely reciting "the modified OPGL polypeptide has modifications", "which are introduced between the preserved B-cell epitopes", or "at least one modification in the form of at least one foreign T helper lymphocyte epitope", does not provide sufficient written description and evidence of procession of the claimed genus. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required.

Claim Objections

Claim 65 is objected to because of the following informalities: Claim 65 recites the same formula number "(I)" as claim 1. However, these formulas are different. Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
July 5, 2006

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